FORM PTO-1082

Date: June 17, 1997

Case Docket No. WC103DIV 20260/10

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application of
Inventors: Lisbeth Illum
For: SMALL PARTICLE COMPOSITIONS FOR INTRANASAL DRUG DELIVERY

Enclosed are:

☒ 1 page Abstract, 26 pages of Specification, 2 pages of Claims and 3 sheets of Drawings (informal).

☒ A copy of an assignment of the invention to Danbiosyst

☐ A certified copy of a _____ application.

☐ An associate power of attorney.

☒ A verified copy statement to establish small entity status under 37 CFR 1.9 and 37 CFR 1.27.

☐

The filing fee has been calculated as shown below:

	(Col. 1)	(Col. 2)	SMALL ENTITY			OTHER THAN A SMALL ENTITY	
FOR:	NO. FILED	NO. EXTRA	RATE	FEE	OR	RATE	FEE
BASIC FEE				$385	OR		$770
TOTAL CLAIMS	14-20 =	*0	x 11 =	$0	OR	x 22 =	$0
INDEP CLAIMS	1-3 =	*0	x 40 =	$0	OR	x 80 =	$0
☐ MULTIPLE DEPENDENT CLAIM PRESENTED			x130 =	$0	OR	x260 =	$0
			TOTAL	$385	OR	TOTAL	$

* If the difference in Col. 1 is less than zero, enter "0" in Col. 2.

☒ Please charge my Deposit Account No. 01-2507 in the amount of $385.00. A duplicate copy of this sheet is enclosed.

☐ Checks in the amount of $385.00 and $55.00 are enclosed.

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- ☒ Any additional filing fees required under 37 CFR 1.16.
- ☒ Any patent application processing fees under 37 CFR 1.17.

☒ The Commissioner is hereby authorized to charge payment of the following fees during the pendency of this application or credit any overpayment to Deposit Account No. 01-2507. A duplicate copy of this sheet is enclosed.

- ☒ Any patent application processing fees under 37 CFR 1.17.
- ☐ The issue fee set in 37 CFR 1.18 at or before mailing of the Notice of Allowance, pursuant to 37 CFR 1.311(b).
- ☒ Any filing fees under 37 CFR 1.16 for the presentation of extra claims.

Respectfully submitted,

Patrea L. Pabst, Reg. No. 31,284

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Lisbeth Illum

Serial No.: Divisional of U.S.S.N. 08/359,937

Express Mail Label No.: EM470185996US

Date of Deposit: June 17, 1997

Filed: December 20, 1994

For: *SMALL PARTICLE COMPOSITIONS FOR INTRANASAL DRUG DELIVERY*

Assistant Commissioner for Patents
Washington, D.C. 20231

REQUEST FOR FILING A DIVISIONAL APPLICATION
UNDER 37 C.F.R. § 1.60

Sir:

This is a request for filing a Divisional application under 37 C.F.R. § 1.60 of pending prior application Serial No. 08/359,937, filed on December 20, 1994 which is a continuation of Serial No. 08/065,676, filed on May 21, 1993.

I hereby verify that the attached papers are a true copy of what is shown in my records to be the above-identified prior application, including the filed executed declaration, and a copy of the Assignment to Danbiosyst UK Limited. The application includes 1 page of Abstract, 26 pages of Specification, 2 pages of Claims, and 3 sheets of Drawings.

Divisional of U.S.S.N. 08/359,937
Filed: December 20, 1994
REQUEST FOR FILING A DIVISIONAL
APPLICATION UNDER 37 C.F.R. §1.60

Enclosed is a Preliminary Amendment. The inventorship for all the claims in this application are the same.

The prior application was assigned of record to Danbiosyst UK Limited, as recorded at reel 6719, frame 0465-0466.

A Power of Attorney by Assignee of Entire Interest and Revocation of Prior Powers as filed in the prior application is enclosed.

A check in the amount of $385.00 is enclosed to cover the filing fee. The filing fee has been calculated on the basis of the claims remaining after entry of the attached Preliminary Amendment. It is believed that this is the proper filing fee since the application will include **1** independent claim and a total of **14** claims after entry of the Preliminary Amendment.

A Verified Statement Claiming Small Entity Status for Danbiosyst UK Limited was filed in the parent application and such status is still proper.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 01-2507. A duplicate copy of this request is enclosed.

This application is being filed on June 17, 1997, by mailing the application to Commissioner of Patents and Trademarks, Washington, DC 20231 via the United States Postal Service "Express Mail Post Office to Addressee" Service under 37 C.F.R. § 1.10.

The Express Mail Label No. appears in the heading of this paper which is attached to the application papers pursuant to 37 C.F.R. §1.10(b).

I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Date: June 17, 1997

ARNALL GOLDEN & GREGORY LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8794

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.10

I hereby certify that this REQUEST FOR FILING A DIVISIONAL APPLICATION and any documents referred to as attached therein are being deposited with the United States Postal Service on this date, June 17, 1997, in an envelope as "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10, Mailing Label Number EM470185996US, addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.

Eva Mukasa

Date: June 17, 1997

SMALL PARTICLE COMPOSITIONS FOR INTRANASAL DRUG DELIVERY

The present invention relates to drug compositions and more particularly to a small particle drug composition which provides for the uptake of active drug across the nasal mucosa.

There is a need to provide effective absorption of high molecular weight material such as proteins and peptides across biological membranes. Normally such molecules are not taken up by the body if administered to the gastrointestinal tract, the buccal mucosa, the rectal mucosa or the vaginal mucosa or if given as an intranasal system. Because peptide hormones such as insulin and calcitonin have a high molecular weight and are readily decomposed by proteolytic enzymes such as pepsin, aminopeptidases, trypsin and chymotrypsin, not enough is absorbed to display an effective pharmacological effect and accordingly they have been administered by parenteral injection.

However, since the administration by injection causes pain, various attempts have been made to develop alternative methods of administration.

Recent studies with insulin have demonstrated that the absorption of such a compound can be increased if it is given together with a so-called absorption enhancer, such as non-ionic surfactants and various bile salt derivatives. An increased permeability of membranes in the presence of these types of surfactant material is not unexpected, indeed the literature in the field of gastroenterology contains a wide range of such absorption promoters. (For a review see Davis *et al* (editors), Delivery Systems for Peptide Drugs. Plenum Press, New York 1987.) However, such materials will probably not be acceptable for the chronic administration of pharmacological agents because of their irritant effects on membranes. This includes not only the non-ionic

variety of surface active agents but also bile salts and bile salt derivatives (e.g. fusidic acid).

At the present time the nose is being proposed as an alternative route for the delivery of drugs that will act within the systemic circulation. Particular attention is being focused on nature-identical peptides or proteins, or analogues or fragments thereof, produced by recombinant DNA techniques. Other drugs that are being suggested are those that are poorly absorbed orally or are extensively metabolised either in the gastro-intestinal tract itself or are subject to first pass metabolism in the liver. However, most polypeptide drugs show a low bio-availability when administered intranasally.

The rapid clearance of nasal sprays from the nose can probably be considered to be a major factor in influencing loss of drugs from potential absorption surfaces. In addition, in the case of peptides and proteins, enzymatic degradation of the drug and molecular size may also have a role in giving low bioavailabilities.

Our earlier co-pending application WO88/09163 discloses intra-nasal microsphere formulations containing an enhancer and our earlier co-pending application WO89/0327 discloses intra-nasal microsphere formulations containing drugs of molecular weight below 6000 which do not require an enhancer. In both of these applications, the diameter of the microspheres is in the range 10 μm to 100 μm. EP 122 036 (Teijin Ltd.) discloses powdery formulations for nasal administration in which at least 90 wt % of the particles have an effective diameter ranging from 10 μm to 250 μm.

It is taught in the art that particles for nasal delivery should be of diameter greater than 10 μm. EP 122 036 states that in compositions in which more than 10 wt % of the particles are below 10 μm, more particles will go further

into the lungs or escape from the nostrils. It is known to use particles of diameter less than 10 μm for delivery of drugs to the lungs. GB 1 381 872 and GB 1 520 248 (Fisons) describe powdery compositions of particles less than 10 μm which are administered by oral inhalation to the lungs.

It has now been found, surprisingly, that bio-adhesive microspheres of diameter less than 10 μm can be used effectively and advantageously to deliver drugs to the nasal mucosa.

A first aspect of the invention therefore provides a drug delivery composition for intranasal delivery comprising a plurality of bioadhesive microspheres and a systemically active drug, at least 90 wt % of the microspheres having a diameter of 0.1 μm or more but less than 10μm. The drug can be contained in the microspheres, admixed with the microspheres or absorbed onto the microspheres. The term "bioadhesive" as used herein is defined as a substance which adheres to the nasal mucosa, preferably to a greater extent than microcrystalline cellulose. It is thought that such bioadhesive microspheres interact with the glycoproteins in the mucus and/or the epithelial cells. The term "drug" is used to embrace any pharmacologically active agent, including hormones, polypeptides and vaccines or components thereof, for example isolated antigens or antigenic parts or mimics thereof.

For any particulate system consisting of a distribution of particle sizes, it is important to define exactly the way in which the diameter is measured. A powder system produced by milling or emulsification followed by suitable processing to yield microspheres (this includes both powders and bioadhesive microspheres) is expected to follow a so-called log normal distribution. Particle size measured by microscopic observation will give a number average distribution. This can be converted to a weight distribution (number-weight, mean diameter), using equations found in standard text books such as T. Allen,

Particle Size Measurement second edition, Chapman and Hall, 1974 and Caserett, L. J. in Toxicology, edited by Casarett, L. J. and Doull, J., Macmillan, New York, 1975, chapter 9.

In the latter, it is stated that the customary expression of particle size is in terms of the median size, either count or mass. For a log normally distributed powder, conversion between a count median diameter (CMD) and a mass median diameter MMD is easily accomplished by a simple calculation where δg is the geometric standard deviation:

$$\log M \text{ (Count)} = \log M' \text{ (Mass)} - 6.9 \log^2 \delta g$$

The weight distribution can be measured directly by screening or sieving or by sedimentation balance. Details are given in the book by Allen (see above).

For a spherical particle, size is uniquely defined and it is possible to talk about a mean diameter. However, with non-spherical particles it is necessary to consider an effective diameter as the size of a sphere that corresponds to the particle under the chosen conditions of measurement. The various options are discussed in the book by T. Allen, where derived diameters are determined by measuring a size dependent property of the particle and relating it to a linear dimension. Effective diameter has been defined by Teijin, so far as it applies to their nasal delivery system, in EP 23359. They refer to a diameter as determined by the opening sizes of sieves. For example, a powder having an effective particle diameter (d) of $37 < d \leq 44$ passes through a sieve having an opening size of 44 microns but does not pass through a sieve having an opening size of 37 microns.

A vibratory sieve may be used when the effective particle diameter of a powder is more than 37 microns, and a sonic sieve (Micro Hand Sifter SWM-2, a

product of Tsutsui Rikagaku Kikai Co. Ltd.) may be used when the effective particle diameter of a powder is not more than 37 microns. It is believed that this definition also applies to EP 122 036 (Teijin Ltd.).

Thus, 90 wt % by weight of spherical microspheres of the present invention have a true mean weight diameter of less than the 10μm effective diameter of the Teijin particles. Preferably 90 wt% of the microspheres are over 0.5 μm in diameter, more preferably over 1.0μm and most preferably over 2 μm in diameter. Suitably, 95 wt % or 99 wt % of the particles satisfy one or more of these criteria.

Preferably the microspheres are prepared from a bio-compatible material that will gel in contact with the mucosal surface. Substantially uniform solid microspheres are preferred. Starch microspheres (cross-linked if necessary) are a preferred material. Other materials that can be used to form microspheres include starch derivatives, modified starches such as amylodextrin, gelatin, albumin, collagen, dextran and dextran derivatives, polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid and derivatives thereof such as benzyl and ethyl esters, gellan gum and derivatives thereof such as benzyl and ethyl esters and pectin and derivatives thereof such as benzyl and ethyl esters. By the term "derivatives" we particularly mean esters and ethers of the parent compound that can be unfunctionalised or functionalised to contain, for example, ionic groupings.

Suitable starch derivatives include hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch, succinate derivatives or starch and grafted starches. Such starch derivatives are well know and described in the art (for example Modified Starches: Properties and Uses, O.B. Wurzburg, CRC Press Boca Raton (1986)).

Suitable dextran derivatives include diethylaminoethyl-dextran (DEAE-dextran), dextran sulphate, dextran methyl-benzylamide sulphonates, dextran methyl-benzylamide carboxylates, carboxymethyl dextran, diphosphonate dextran, dextran hydrazide, palmitoyldextran and dextran phosphate.

Preparation of these microspheres is well described in the pharmaceutical literature (see for example Davis "Microspheres and Drug Therapy", Elsevier Biomedical Press, 1984, which is incorporated herein by reference). Emulsion and phase separation methods are both suitable. For example, albumin microspheres may be made using the water-in-oil emulsification method where a dispersion of albumin is produced in a suitable oil by homogenization techniques or stirring techniques, with the addition if necessary of small amounts of an appropriate surface active agent.

The size of the microspheres produced is a function of the speed of stirring or homogenization conditions used with the selected mixture of ingredients. By using a stirring speed or homogenization within the range 100-10000rpm, microspheres within the desired size range of 0.1μm to 10μm will be produced. It is within the scope of the person skilled in the art to select the exact conditions for the desired microsphere size. The agitation can be provided by a simple laboratory stirrer or by more sophisticated devices such as a microfluidizer or homogenizer. The microspheres obtained may be sieved if necessary in order to remove the occasional over- or under-sized microsphere. This may also be done using other size spearation techniques, such as air elutriation.

Emulsification techniques are also used to produce starch microspheres as described in GB 1 518 121 and EP 223 303 as well as for the preparation of microspheres of gelatin. Proteinaceous microspheres may also be prepared by coacervation methods such as simple or complex coacervation or by phase separation techniques using an appropriate solvent or electrolyte solution. Full

details of the methods of preparing these systems can be obtained from standard text books (see for example Florence and Attwood, Physicochemical Principles of Pharmacy 2nd Ed., MacMillan Press, 1988, Chapter 8).

The following examples demonstrate preparation of microspheres within the desired size range of 0.1μm to 10μm.

Preparation of hyaluronic acid ester microspheres by solvent extraction

An emulsion was formed by mixing a 6% w/v solution of the polymer eg benzyl hyaluronic acid ester (Hyaff- 11) in dimethylsulphoxide with white mineral oil containing 0.5% Arlacel A. The inner phase was added to the outer oil phase (their respective ratio is 1 : 16 v/v) with continuous stirring for 10 minutes (1000 rpm). Ethyl acetate, the extraction solvent was then added to the emulsion at a ratio of 2 : 1 v/v. The extraction proceeds for 15 minutes at a stirring rate of 700 rpm until the microparticles are formed. The microsphere suspension was filtered and extensively washed with n-hexane and dried. Drug can be incorporated into the microspheres by addition to the initial polymer solution. The obtained size of microspheres was 2-10 μm.

The preparation of small starch microspheres using emulsification

A 10% starch gel was prepared by heating (70°C) 5 g of starch with 40 ml of water until a clear gel was formed. After cooling water was added to a volume of 50 ml. 20 ml of this starch gel was then added to 100 ml of soya oil BP containing antioxidant and 1% v/v Span 80 and homogenised at 7000 rpm for 3 minutes. This emulsion was then added to 100 ml hot (80°C) soya oil BP (containing antioxidant) and stirred at 1500 rpm with a paddle stirrer while heated to 115°C over 15 minutes. The emulsion was left stirring at 115°C for 15 minutes and then rapidly cooled by packing in ice while stirring. 100 ml

of acetone was added and the microspheres were centrifuged at 4500 rpm for 15 minutes. The pellet was resuspended in acetone and separated into the desired size fraction by filtering through an appropriate sieve, for example a 0.5μm fluoropore filter. The microspheres were then allowed to air dry. The microspheres produced were $< 10\mu$m diameter.

Production of small albumin microspheres

Albumin microspheres were produced by a modification of the method described by Ratcliffe *et al* (1984) *J. Pharm. Pharmacol.* 36, 431-436, which is incorporated herein by reference. One ml of 5% human serum albumin or ovalbumin at pH 6.8 was added to 25 ml of olive oil or light mineral oil with or without 0.25 ml of Span 85. The mixture was stirred in a mix-cell for 10 min under turbulent flow conditions to form a w/o emulsion, using a mechanical stirrer (Heidolph) at 775 rpm (Tachometer DOT 1, Compact Instruments). Glutaraldehyde solution 25% (w/v) was added to 3.6% (v/v) of aqueous phase and the emulsion stirred for a further 30 min to denature and cross-link the albumin. The microspheres were collected by centrifugation at 2500 g for 20 min. The oil was then removed and the spheres washed with diethyl ether followed by ethanol. The microspheres were collected by decantation. The microspheres produced were in the size range 0.1 - 10μm.

Production of small starch microspheres

5 g potato starch were dissolved in 95 ml of water at about 90°C. A second solution was prepared from 3 g of polyethylene glycol (m_w=6000) and 47 ml of water. This solution was heated to about 70°C, whereafter the warm starch solution was added while stirring, to form an emulsion. When the two-phase system had formed (with the starch solution as the inner phase) the mixture was allowed to cool to room temperature under continued stirring, whereupon the

inner phase was converted to gel particles. The particles were filtered off at room temperature and stirred in 100 ml of ethanol, whereafter the particles were again filtered off and laid to dry in air. The yield was 90% and the microspheres produced were $< 10\mu$m diameter.

The final microspheres can be modified by chemical cross-linking or heat treatment if desired.

The preparation of small albumin microspheres using an emulsification technique and heat stabilisation

The following non-limited example illustrates the use of heat stabilisation. This is particularly suitable for albumin microspheres but can be used with any other microspheres according to the invention.

100 ml Soya oil was mixed with 1 ml of a 10% albumin solution and homogenised at 6000 rpm. The emulsion was added to 200 ml soya oil at 50°C and stirred at 1500 rpm. The emulsion was then heated to 120°C and equilibrated for 20 minutes at this temperature. The microspheres were then cooled to room temperature and washed with petroleum ether. The microspheres were then centrifuged at 4500 rpm for 15 minutes and the collected pellet was washed with ethanol followed by acetone. The microspheres were then filtered and allowed to air dry. Microspheres of 1-10μm were prepared.

The preparation of small abbumin microspheres using an emulsification technique and chemical crosslinking

The following non-limiting example is presented as one example of a method of preparing a microsphere which is modified by cross-linking.

100 ml Soya oil was mixed with 1 ml of a 10% albumin solution and homogenised at 6000 rpm. The emulsion was added to 200 ml soya oil at 50° and stirred at 1500 rpm.

To crosslink the microspheres, 100 μl of a 25% Glutaraldehyde solution was added dropwise and the emulsion stirred at 1500 rpm for a further 30 minutes. The microspheres were harvested by added petroleum ether, centrifuging and washing with petroleum ether.

The microspheres were then centrifuged at 4500 rpm for 15 minutes and the collected pellet was washed with ethanol followed by acetone. The microspheres were then filtered and allowed to air dry. Microspheres of 1-10μm were prepared.

Suitable cross-linking agents for use with starch microspheres include epichlorohydrin, terephthaloyl chloride and sodium trimetaphosphate. Suitable agents for use with albumin microspheres include aldehydes such as formaldehyde and glutaraldehyde, oxidised dextran ("dextranox") and 2,3-butanediose, the latter also being suitable for use with gelatin microspheres. Agents such as N,N,N^1,N^1-tetramethylethylenediamine can be used with dextran microspheres.

The active agent can be incorporated into the microspheres during their formulation or sorbed into-onto the system after preparation. The effectiveness of the system can be controlled by the physical nature of the microsphere matrix and, for example, the extent of cross linking.

As an added advantage the particles may have variable controlled release characteristics through modifications made to the microsphere system, for example by controlling the degree of cross-linking or by the incorporation of

excipients that alter the diffusional properties of the administered drug. It has been found that by increasing the heat stabilisation time or the time of exposure to the cross-linking agent during microsphere preparation, the release of the drug from the microsphere is delayed.

The amount of drug that can be carried by the microspheres is termed the loading capacity, which is determined by the physico-chemical properties of the drug molecule and in particular its size and affinity for the particle matrix. Higher loading capacities are to be expected when the administered drug is incorporated into the microspheres during the actual process of microsphere manufacture. It is known that for many peptides and proteins the amount of drug substance to be administered for a resultant therapeutic effect will be of the order of a few micrograms or less.

Microcapsules of a similar size, which are bioadhesive and which have controlled release properties, may also provide similar benefit in terms of an increased and modified bio-availability of administered drugs. These microcapsules can be produced by a variety of methods. The surface of the capsule can be adhesive in its own right or can be modified by coating methods familiar to those skilled in the art. These coating materials are preferably bioadhesive polymers such as polycarbophil, carbopol, DEAE-dextran or alginates. These microcapsules are deemed to be "microspheres" for the purposes of this specification and, again, are more than 0.1 μm in diameter but less than 10 μm.

Using the combination of microspheres and drug, it has been found that the bioadhesive microsphere systems have the ability to enhance greatly the bioavailability of drugs, especially polar drugs, when they are administered together.

This potentiation of effect is believed to be due to the greater retention of the delivery systems in the nasal cavity.

The microsphere composition can also afford protection of the drug against degradation by enzymes.

The drug delivery system of the invention may advantageously comprise an absorption enhancer. By "enhancer", we mean any material which acts to increase absorption across the mucosa. Such materials include mucolytic agents, degradative enzyme inhibitors and compounds which increase permeability of the mucosal cell membranes. Whether a given compound is an "enhancer" can be determined by comparing two formulations comprising a non-associated, small polar molecule as the drug, with or without the enhancer, in an in vivo or good model test and determining whether the uptake of the drug is enhanced to a clinically significant degree. The enhancer should not produce any problems in terms of chronic toxicity because in vivo the enhancer should be non-irritant and/or rapidly metabolised to a normal cell constituent that does not have any significant irritant effect.

Preferred enhancing materials lysophospholipids, for example lyso-phosphatidylcholine obtainable from egg or soy lecithin. Other lysophosphatidylcholines that have different acyl groups as well as lyso compounds produced from phosphatidylethanolamines and phosphatidic acid which have similar membrane modifying properties may be used. Acyl carnitines (e.g. palmitoyl-dl-carnitine-chloride) is an alternative. A suitable concentration is from 0.02 to 20% w/v.

Other enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the

SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethyl-acetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.

The same concept of delivery of a drug incorporated into or onto a bioadhesive microsphere with an added pharmaceutical adjuvant applies to systems that contain active drug and mucolytic agent, peptidase inhibitors or non-drug polypeptide substrate singly or in combination. Suitably mucolytic agents are thiol-containing compounds such as N-acetylcysteine and derivatives thereof. Peptide inhibitors include actinonin, amastatin, bestatin, chloroacetyl-HOLeu-Ala-Gly-NH_2, diprotin A and B, ebelactone A and B, E-64, leupeptin, pepstatin A, phisphoramidon, H-Thr-(tBu)-Phe-Pro-OH, aprotinin, kallikrein, chymostatin, benzamidine, chymotrypsin and trypsin. Suitable concentrations are from 0.01 to 10% w/v. The person skilled in the art will readily be able to determine whether an enhancer should be included.

The microsphere composition may be used with drugs selected from the following non-exclusive list: insulin, calcitonins (for example porcine, human, salmon, chicken, or eel) and synthetic modifications thereof, enkephalins, LHRH and analogues (Nafarelin, Buserelin, Zolidex), GHRH (growth hormone releasing hormone), nifedipin, THF(thymic humoral factor), CGRP (calcitonin gene related peptide), atrial natriuretic peptide, antibiotics, metoclopramide, ergotamine, Pizotizin, nasal vaccines (particularly HIV vaccines, measles, rhinovirus Type 13 and respiratory syncitial virus), pentamidine, CCK (Cholecystikinine), DDVAP, Interferons, growth hormone (solatotropir polypeptides or their derivatives (preferably with a molecular weight from 100 to 300000), secretin, bradykinin antagonists, GRF (Growth releasing factor),

THF, TRH (Thyrotropin releasing hormone), ACTH analogues, IGF (Insuline like growth factors), CGRP (Calcitorin gene related peptide) Atrial Natriuretic peptide, Vasopressin and analogues (DDAVP, Lypressin), Metoclopramide, Migraine treatment (Dihydroergotamine, Ergometrine, Ergotamine, Pizotizin), Nasal Vaccines (Particularly AIDS vaccines) FACTOR VIII, Colony Stimulating factors, G-CSF (granulocyte-colony stimulating factor), EPO (Erythropoitin) PTH (Parathyroid hormone).

Further drugs include: antibiotics and antimicrobial agents such as tetracyline hydrochloride, leucomycin, penicillin, penicillin derivatives, erythromycin, gentamicin, sulphathiazole and nitrofurazone; local anaesthetics such as benzocaine; vasoconstrictors such as phenylephrine hydrochloride, tetrahydrozoline hydrochloride, naphazoline nitrate, oxymetazoline hydrochloride and tramazoline hydrochloride; cardiotonics such as digitalis and digoxin; vasodilators such as nitroglycerine and papaverine hydrochloride; antiseptics such as chlorhexidine hydrochloride, hexylresorcinol, dequaliniumchloride and ethacridine; enzymes such as lysozyme chloride, dextranase; bone metabolism controlling agents such as vitamin D, active vitamin D and vitamin C; sex hormones; hypotensives; sedatives; anti-tumour agents; steroidal anti-inflammatory agents such as hydrocortisone, prednisone, fluticasone, prednisolone, triamcinolone, triamcinolone acetonide, dexamethasone, betamethasone, beclomethasone, and beclomethasone dipropionate; non-steroidal anti-inflammatory agents such as acetaminophen, aspirin, aminopyrine, phenylbutazone, medanamic acid, ibuprofen, diclofenac sodium, indomethacine, colchicine, and probenocid; enzymatic anti-inflammatory agents such as chymotrypsin and bromelain seratiopeptidase; anti-histaminic agents such as diphenhydramine hydrochloride, chloropheniramine maleate and clemastine; anti-allergic agents and antitussive-expectorant antasthmatic agents such as sodium chromoglycate, codeine phosphate, and isoproterenol hydrochloride.

The molecular weight of the drug is preferably in the range 100 to 300,000.

In order to improve the properties, appearance or odour of the pharmaceutical composition, it may, if desired, contain any of known additives such as colouring agents, preservatives, antiseptics, etc. Examples of colouring agents include ß-carotene, Red No. 2 and Blue No. 1; examples of preservatives include stearic acid, ascorbyl stearate and ascorbic acid; examples of antiseptics include p-hydroxy-benzoate, phenol, chlorobutanol, benzylkonium chloride etc.; and examples of corrigents include menthol and citrus perfume.

A further embodiment of the invention provides a system for intranasal drug delivery comprising a drug delivery composition and container having an orifice through which the composition can be delivered to the nasal mucosa in a gas stream. The gas stream may be air or any other physiologically harmless gas. Preferably the means is such that, in use, the product of the flow rate and the square of the microsphere diameter is greater than 2000 μm^2 litres/min.

The means to deliver the microspheres, which are for example in a freeze dried form, to the nasal cavity is conveniently a nasal insufflator device or pressurised aerosol cannister. Examples of these are already employed for commercial powder systems intended for nasal application. The microspheres should be administered in a dry, air-dispensable form.

The insufflator produces a finely divided cloud of the dry powder or microspheres. The insufflator is preferably provided with means to ensure administration of a substantially fixed amount of the composition. The powder or microspheres may be used directly with an insufflator which is provided with a bottle or container for the powder or microspheres. Alternatively the powder or microspheres may be filled into a capsule such as a gelatin capsule, or other single dose device adapted for nasal administration. The in sufflator preferably

has means such as a needle to break open the capsule or other device to provide holes through which jets of the powdery composition can be delivered to the nasal cavity.

The deposition in the nose will depend on two factors: the size of the particles (aerodynamic diameter) and flow rate (F) of inspiratory air.

The controlling factor is (d_a) F where da is measured in microns and F in litres/min.

The product (d_a) ^{2}F should exceed 2000μm^2.litres/min to give the required deposition in the nasal cavity of the total dose. Resting ventilation is of the order of 30 litres/min.

Using the above types of delivery means, the required flow rate will be achieved by taking a rapid inhalation. Sufficient flow rate will not be achieved by merely normal resting ventilation.

Under extreme exertion or rapid inhalation, a very large fraction of the deposition takes place within the anterior non-ciliated part of the nose, where particles are retained for long periods, gradually being dragged along to the nasopharynx by the mucus drag effect. Details of deposition and flow rate studies may be found in the art, for example G.M. Hidy, Aerosols, Academic Press Inc. 1984.

For particulate systems administered to the respiratory tract, it is necessary to consider the aerodynamic diameter that takes into account the size of the particle and its density. For example, a particle with a physical diameter of 0.5 μm and density of 10 will behave like a larger particle (of greater than 2 microns) of unit density. This applies strictly to spherical particles and may be

varied markedly by the shape of the particle. The aerodynamic (kinetic diameter) has been defined as the diameter of a hypothetical sphere of unit density having the same terminal settling velocity as a particle in question regardless of its geometric size, shape and true density.

The small microspheres of the present invention have been found to be easier to administer using available devices, especially those working on the basis of pressure packs and accurate valves and actuators, as fewer problems with blockages occur.

Small microspheres are also easier to fluidize in powder administration devices, such as insufflators.

The narrower size range has been found to give a more uniform dose for an active material such as a peptide. The narrower size range has also been found to minimize separation of large and small particles on storage and transport and during administration. The admixture of insulin and microcrystalline cellulose as described in the prior art such as EP 122 036 results in a system that can undergo separation of particles on storage, shipment and administration. For example, when evaluated using an Andersen Impactor, the insulin was found largely in the smaller size fractions and the cellulose in the larger fractions. This could lead to non-uniformity of dosing and unpredictive absorption. Greater control over the deposition site in the nose can be achieved with smaller and more uniform particles.

Preferred aspects of the invention will now be illustrated by way of example and with reference to the accompanying drawings, in which:

Figure 1 shows the results of Example 1, illustrating intranasal administration of insulin at 2 IU/kg with 2 mg/kg of differently sized microspheres in sheep.

Figure 2 shows the results of Example 2, illustrating the clearance of intranasally-administered, radiolabelled, large and small microsphere formulations and a liquid formulation, in humans.

Figure 3 shows the results of Example 3 illustrating the effect of intranasal administration of insulin with small ($<10\mu$m) hyaluronic acid microspheres compared with large starch microspheres in sheep.

EXAMPLE 1: Comparative Biological Data (sheep)

Summary. Insulin was administered nasally to sheep at 2 IU/kg as a lyophilised powder with either starch microspheres 45/25 (SMS 45/25) or smaller (< 10 microns) starch microspheres BR 71B 03C (SSMS BR 71B) at 2 mg/kg. After an initial small rise in both groups, the plasma glucose concentrations were generally lower after SSMS BR 71B co-administration. The lowest concentrations reached after SSMS BR 71B and SMS 45/25 co-administration were 82.0% and 86.2% of control at 150 minutes after dosing.

Materials and Methods

Semi-synthetic human Na-insulin (Nordisk, Gentofte, Batch No P389, 28 IU/mg) was used. The water content of the sample was determined by spectrophotometry, and the material was found to be 84.4% pure. Starch microspheres 45/25, Batch Number 49238) and smaller (< 10 microns) starch microspheres BR 71B 03C (SSMS BR 71B, Batch Number 97327b), were supplied by Pharmacia.

Ultra pure water ("Elgastat UHP", Elga) was used throughout and all other reagents were at least of standard laboratory grade.

Sheep. Eight male cross-bred sheep weighing (± SEM) 29.0 ± 1.07 kg were used. The sheep were normally housed indoors, and remained inside for the duration of the study. Animals were not fasted prior to insulin administration. An in-dwelling Viggo secalon cannula of 1.2 mm id, fitted with a secalon universal flow-switch, was placed approximately 15 cm into one of the external jugular veins of each animal on the first day of the study and, whenever necessary, kept patent by flushing it with heparinised (25 IU/ml) 0.9% saline solution. This cannula was removed upon the completion of the study and the sheep were returned to their normal housing.

Preparation of insulin formulations. For the preparation of these lyophilised microsphere formulations, a solution of 50.8 mg insulin in 50 ml of water (1.016 mg/ml, 24 IU/ml) was prepared. The required quantity of each of the microspheres, SMS 45/25 or SSMS BR 71B (480 mg), was dispersed in 20 ml of insulin solution plus 12 ml of water (to keep the ratio of microspheres to solution at 15:1 [mg:ml]). The two resultant suspensions were stirred for one hour at room temperature and then freeze-dried to obtain the powder formulations (Formulations 1 and 2). The freeze-drying was performed on an Edwards Modulyo freeze-dryer fitted with a bell-jar assembly and operated at a pressure of 0.08 torr (10.7 N/m^2), a condenser temperature of -53°C and a product shelf temperature of approximately 20°C. The freeze-drying process was allowed to proceed for 24 hours, after which the final product was loaded into the administration devices and then stored with dessicant at 4°C for 16 hours prior to administration to the sheep.

Administration of insulin formulations and blood sampling. The sheep were divided into two groups of four animals each. Group 1: Four animals received 2.0 IU/kg insulin together with 2.0 mg/kg SMS 45/25 microspheres (Formulation 1) intranasally in the form of a lyophilised powder. A sheep of 30 kg thus received 60 IU of insulin together with 60 mg SMS 45/25

microspheres. Group 2: Four animals received 2.0 IU/kg insulin together with 2.0 mg/kg SSMS BR 71B microspheres (Formulation 2) intranasally in the form of a lyophilised powder. A sheep of 30 kg thus received 60 IU of insulin together with 60 mg SSMS BR 71B microspheres.

The sheep were sedated with an iv dose of ketamine hydrochloride (Ketalar$^{(R)}$, 100 mg/ml injection) at 2.25 mg/kg and this anaesthesia lasted for about 3 minutes. This treatment acted as an animal restraint, and also as a counter-measure against the animal sneezing during administration. For intranasal administration a Leymed red rubber Magill's tube oral of 6.5 mm was loaded with the powder formulation and then inserted into the nostril of the sheep to a preset depth of 6 cm before blowing the powder into the nasal cavity. Blood samples of 6.0 ml were collected onto crushed ice from the cannulated jugular vein of the sheep at 15 and 5 minutes prior to the insulin administration and at 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180 and 240 minutes post-administration. Each blood sample was divided into two parts. For insulin analysis, the blood collected (4.0 ml) was mixed gently in 4 ml heparinised tubes (Lithium Heparin, 60 IU, Sarstedt, Leicester, UK). For glucose analysis, the blood collected (2.0 ml) was mixed gently in 2 ml sodium fluoride tubes (2.0 mg fluoride and 30 IU heparin, Sarstedt, Leicester, UK). The plasma was separated by centrifugation at 4°C and 3200 rpm, and then stored at -20°C awaiting insulin and glucose analysis within our Analytical Section.

Analysis. Plasma glucose concentrations were analysed by the glucose oxidase method using a Yellow Springs 23 AM glucose analyser (Yellow Springs, Ohio, USA). Plasma insulin was not measured at this stage.

Results and discussion. The mean changes in plasma glucose following the co-administration of insulin with SMS 45/25 or SSMS BR 71B are plotted on the same axes in Figure 1.

Both SMS 45/25 and SSMS BR 71B groups showed an initial rise in plasma glucose concentrations up to approximately 105.0% of the controls at approximately 20-30 minutes after dosing. Thereafter, concentrations of glucose steadily fell to a low point at approximately 150 minutes after dosing. At this low point the change in glucose concentration was greatest after co-administration of SSMS BR 71B (82.0%) than after co-administration of SMS 45/25 (86.2%). Indeed, after co-administration of SSMS BR 71B the glucose concentrations were generally lower than those after SMS 45/25 co-administration.

The area under the curve (AUC) is a particularly important measure of the effectiveness of the enhancer system: Group 1 gave a mean AUC of 1704% per minute, whereas Group 2 gave a mean AUC of 2766% per minute. This is a 62% increase in AUC, and was accompanied by a 25% increase in the blood concentration of insulin.

EXAMPLE 2: Comparative Biological Data (human)

Small starch microspheres were labelled with Tc99m using the stannous chloride technique and freeze dried. Doses of 30 mg were filled into hard gelatin capsules for the application. A group of healthy male and female volunteers (n=3) were each given the microsphere preparation using a Lomudal nasal insufflator. The total content of the capsules was applied during inhalation to the mucosal surface of either the right or the left nostril. The deposition and the subsequent clearance of the formulation were followed by gamma scintigraphy while the volunteers were positioned in an upright position with the nose in a fixed position close to the collimator surface of the camera, using a specially designed template. Static views were recorded at times 0, 10, 30, 45, 90, 120, 180 and 240 min after administration. Regions of interest were drawn around the initial site of deposition and the total nasal cavity. The

counts from each region were corrected for background counts and radioactive decay and expressed as a portion of the registered activity in the initial deposition site.

Fig 2 shows a comparison between the clearance of small starch microspheres and large microspheres and a simple control solution. It can be seen that the half time of clearance for the small microspheres has not been reached within the time of the study, whereas the half time of clearance for the large microspheres is 180 min as compared to 15 min for the solution formulation.

Hence the use of the small microspheres (1-10 μm) as compared to the large microspheres (40 μm) gives a significantly longer residence time in the nasal cavity.

EXAMPLE 3: Investigation of the effect of different small hyaluronic acid microsphere formulations on the intranasal absorption of insulin by sheep

The example investigates the effect of two different types of small ($< 10\mu$m) hyaluronic acid microspheres (HYAFF 11 and HYAFF 11 - dextran) on the nasal absorption of insulin. The results were compared with two control groups which were dosed either, nasally with insulin and large starch microspheres, or subcutaneously with insulin solution alone.

Materials and methods

Materials Semi-synthetic human Na-insulin (28 IU/mg) was used. The water content of the sample was determined by spectrophotometry at the time of use, and this purity was used for all subsequent calculations.

Hyaluronic acid microspheres HYAFF 11, ($< 10\mu m$) prepared from the benzyl ester of hyaluronic acid (Batch number 102H11R), and HYAFF 11 - dextran (Batch Number 100H11RDex) ($< 10\mu m$) supplied by Fidia, were used.

Starch microspheres 45/25 ($45\mu m$ swollen/$25\mu m$ dry), (SMS, Batch Number 49238), from Pharmacia were used.

Ultra pure water ("Elgastat UHP", Elga) was used throughout.

All other reagents were, at least, of standard laboratory grade.

Sheep Sixteen sheep were used in this study.

The sheep were normally housed indoors, and remained inside for the duration of the study. The animals were not fasted prior to insulin administration. An in-dwelling cannula fitted with a flow-switch, was placed into one of the external jugular veins of each animal on the first day of the study and, whenever necessary, was kept patent by flushing it with heparinised saline solution. This cannula was removed upon the completion of the study, and the sheep were returned to their normal housing.

Preparation of insulin formulations For the preparation of the lyophilised microsphere formulations a solution of approximately 130 IU/ml (4.6 mg/ml) of pure insulin in water was prepared. The required quantity of each of the

microspheres was dispersed in water and sonicated for 30 seconds. The appropriate volume of insulin solution was added to each microsphere suspension, and the volume adjusted with water to keep the ratio of microspheres to solution constant. The three resultant suspensions were stirred at room temperature, and then freeze-dried to obtain the powder formulations (Formulations 1 to 3). The freeze-drying process was allowed to proceed to completion, after which the final product were loaded into the administration devices and then stored, with dessicant, at 4°C for 16 hours prior to administration to the sheep.

On the day of dosing the subcutaneous dosing solution (Formulation 4) was prepared comprising a solution of 10 IU/ml (0.357 mg/ml) of pure insulin in 0.9% saline.

Administration of insulin formulations The sheep were divided into four groups of four animals each and treated as shown in Table 1.

Table 1. Dose groups

GROUP FORMULATIONS	DOSES PER kg INSULIN (IU/mg)	MICROS. (mg)	ACTUAL DOSES SHEET	INSULIN (IU/mg)	MICROS (mg)
1. HYAFF 11	2.0/0.071	2.0	A	72/2.571	72
			B	92/3.286	92
			AF	76/2.714	76
			BF	70/2.500	70
2. HYAFF 11 - dextran	2.0/0.071	2.0	C	82/2.929	82
			D	82/2.929	82
			CF	70/2.500	70
			DF	74/2.643	74
3. SMS	2.0/0.071	2.5	E	64/2.286	80
			F	78/2.786	97.5

			EF	74/2.643 92.5
			FF	58/2.071 72.5
4. S/C Insulin alone	0.2/0.007	---	G	6.8/0.243---
			GF	6.6/0.236---
			H	6.8/0.243---
			HF	8.8/0.314---

For intranasal administration of the powder formulations (1 to 3) a tube was loaded with the formulation and then inserted into the nostril of the sheep to a preset depth, before blowing the powder into the nasal cavity. Subcutaneous injections were made into a shaved site at the neck, using a suitable syringe. The dose volume was 0.02 ml/kg.

Sedation/Blood Sampling The sheep were sedated using an intravenous dose of ketamine hydrochloride. This was intended for animal restraint, and also as a counter-measure against the animal sneezing during administration. (Sheep D did sneeze soon after administration). The anaesthesia lasted for about 3 minutes. Blood samples of 4.0ml were collected onto crushed ice from the cannulated jugular vein of the sheep at 15 and 5 minutes prior to the insulin administration and at 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180 and 240 minutes post-administration. Blood samples were mixed gently in 4 ml heparinised tubes. The plasma was separated by centrifugation and each plasma sample was divided into two aliquots of approximately 1 ml. The plasma was then stored at -20°C awaiting analysis by our Analytical Section.

Glucose analysis Plasma glucose concentrations were measured using a Yellow Springs YS1 23 AM blood glucose analyser (Yellow Springs. Ohio, USA).

Calculation of results The plasma glucose concentrations were determined as mmol/l. The two control plasma glucose concentrations (-15 and -5 minutes)

for each animal were meaned and all test plasma concentrations were expressed as a percentage of these mean control values. Results are therefore percent of control plasma concentrations.

The area between 100% and the actual blood glucose curve (area of fall from control) was calculated using the trapezoidal method.

Results and discussion The mean ($\pm$ SEM) values for the percent of control plasma glucose concentration following administration of insulin nasally with Hyaff 11, Hyaff 11 - dextran or SMS, together with administration via the subcutaneous route, are shown in Figure 3. These results illustrate that all formulations caused a marked decline in plasma glucose concentrations. However, from the results shown in Figure 3, it can be seen that the decrease in plasma glucose level was significantly faster and greater with both of the small ($< 10\mu$m) hyaluronic acid microsphere formulations than with the large starch microsphere formulation.

CLAIMS

1. In a particulate drug delivery composition for intranasal delivery comprising a plurality of bioadhesive microspheres and a systemically active drug, the improvement comprising that at least 90 wt % of the microspheres of the composition have a diameter of between 0.1 μm and 10 μm.

2. A drug delivery composition according to Claim 1 wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface.

3. A drug delivery composition according to Claim 1 or 2 wherein the microspheres comprise starch, starch derivatives, gelatin, albumin, collagen, dextran or dextran derivatives.

4. A drug delivery composition according to Claim 3 wherein the microspheres are starch microspheres.

5. A drug delivery composition according to Claim 1 wherein the microsphere material is cross-linked.

6. A drug delivery composition according to Claim 1 wherein the microspheres have been stabilised by heat treatment.

7. A drug delivery composition according to Claim 1 additionally comprising an absorption enhancer.

8. A drug delivery composition according to Claim 7 wherein the absorption enhancer is a surfactant, a lysophosphatidylcholine or a lysophosphatidylglycerol.

9. A drug delivery composition according to Claim 1 wherein the drug is a biologically active peptide.

10. A drug delivery composition according to Claim 9 wherein the peptide is insulin or calcitonin.

11. A system for intranasal drug delivery comprising a drug delivery composition according to Claim 1 and a container having an orifice through which the composition can be delivered to the nasal mucosa in a gas stream.

12. A system according to Claim 11 wherein the system is such that, in use, the product of the flow rate and the square of the microsphere aerodynamic diameter is greater than 2000 μm^2.litres/min.

13. A method of delivering a drug to the nasal mucosa, comprising introducing a gas stream containing a composition according Claim 1 into the nose.

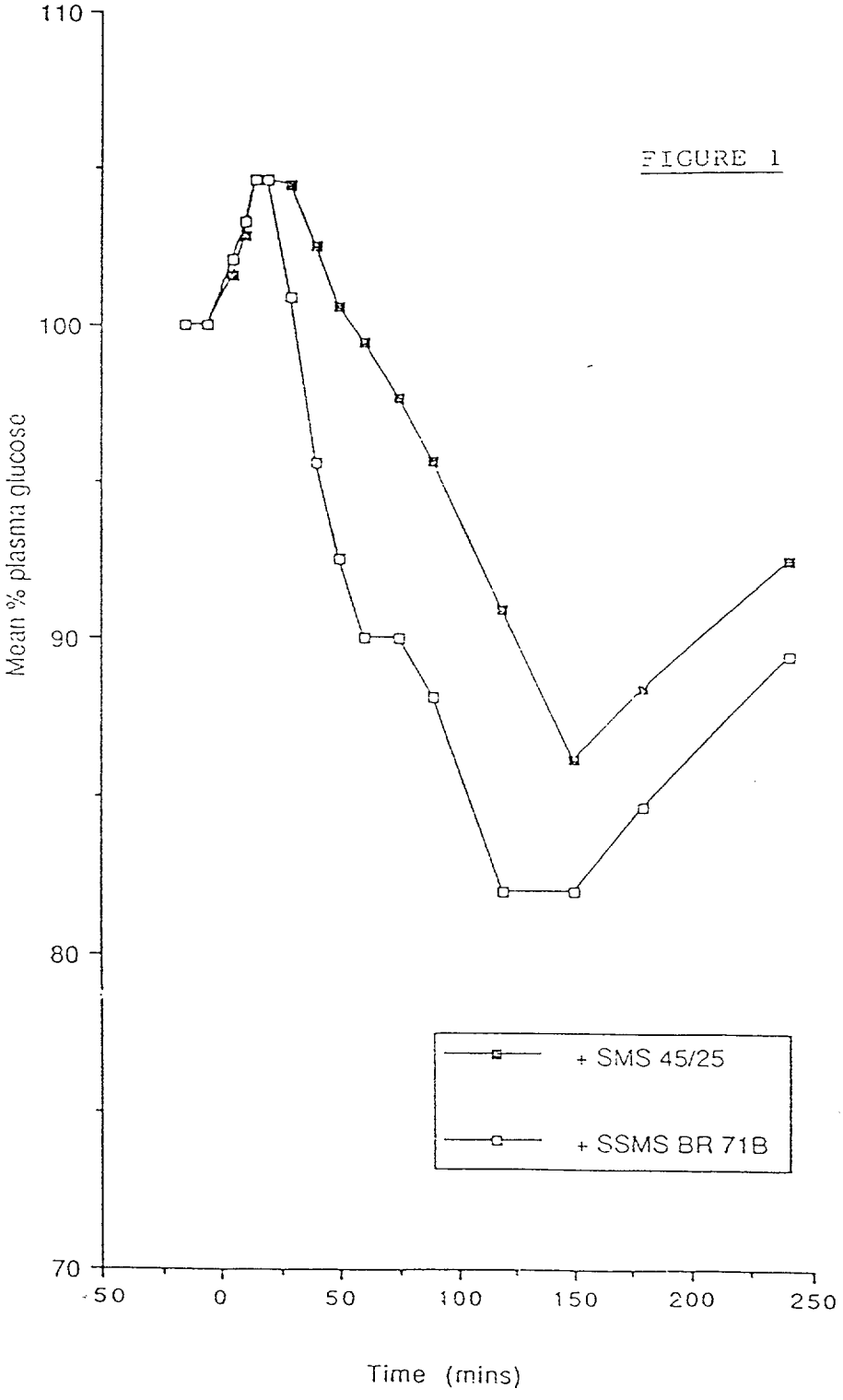
14. A method of treating diabetes comprising introducing a gas stream containing a composition according to Claim 1 wherein the systemically active drug is insulin into the nose.

ABSTRACT

SMALL PARTICLE DRUG COMPOSITIONS

A drug delivery composition for intranasal delivery comprises a plurality of bioadhesive microspheres and active drug associated with each microsphere, at least 90 wt % of the microspheres having a diameter in the range 0.1 μm to 10 μm. The microspheres may be of starch, gelatin, dextran, collagen or albumin. Suitable drugs include peptides, such as insulin, and antigenic vaccine ingredients. The composition may additionally comprise an absorption enhancer. The microspheres are administered to the nasal cavity by a means such that the product of the square of the microsphere diameter and the flow rate is greater than 2000 μm^2.litres/min.

FIGURE 1


110
100
90
80
70
Mean % plasma glucose
-50
0
50
100
150
200
250
Time (mins)
+ SMS 45/25
+ SSMS BR 71B

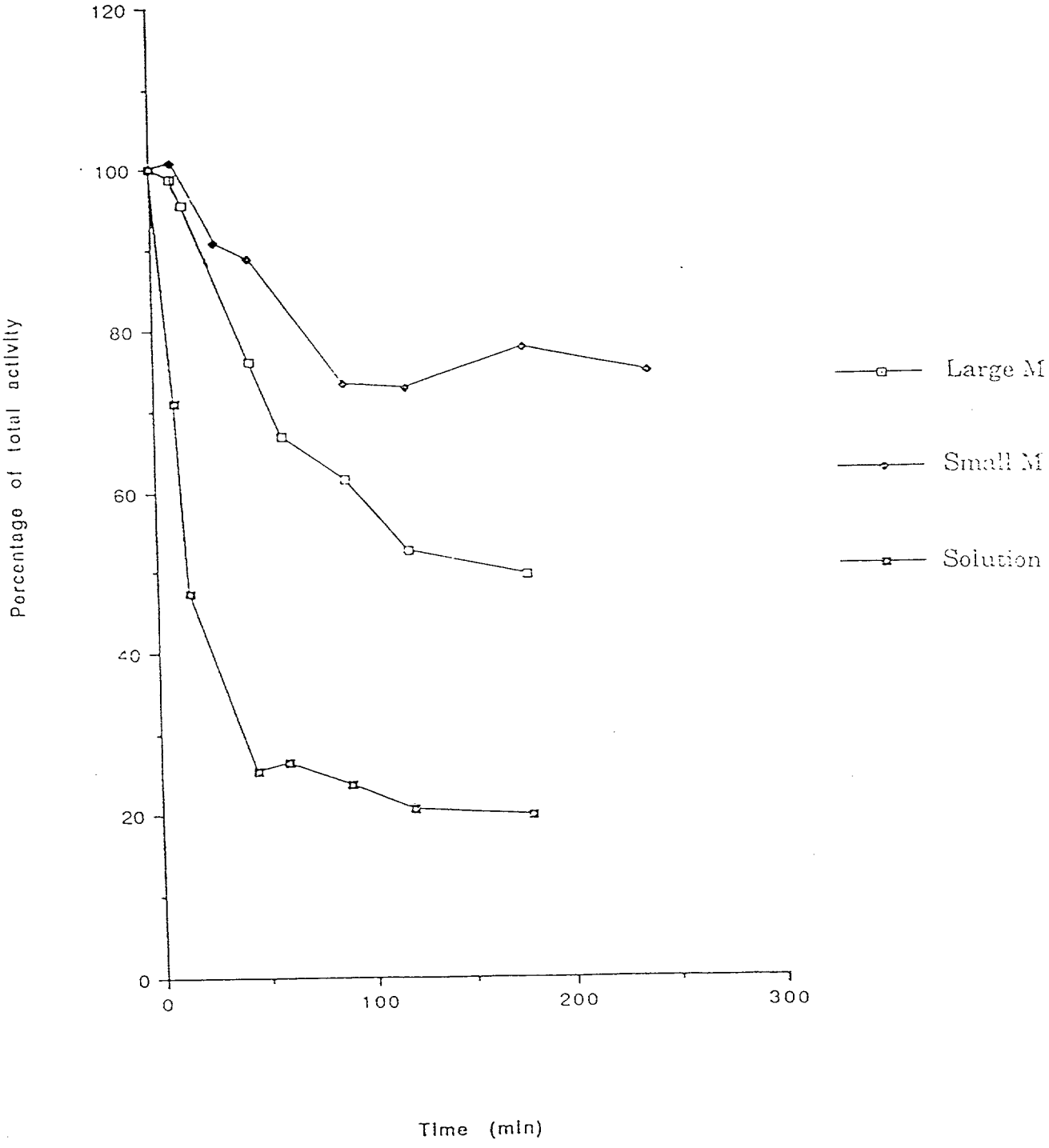

120
100
80
60
40
20
0
0
100
200
300
Percentage of total activity
Time (min)
Large M
Small M
Solution

FIGURE 2

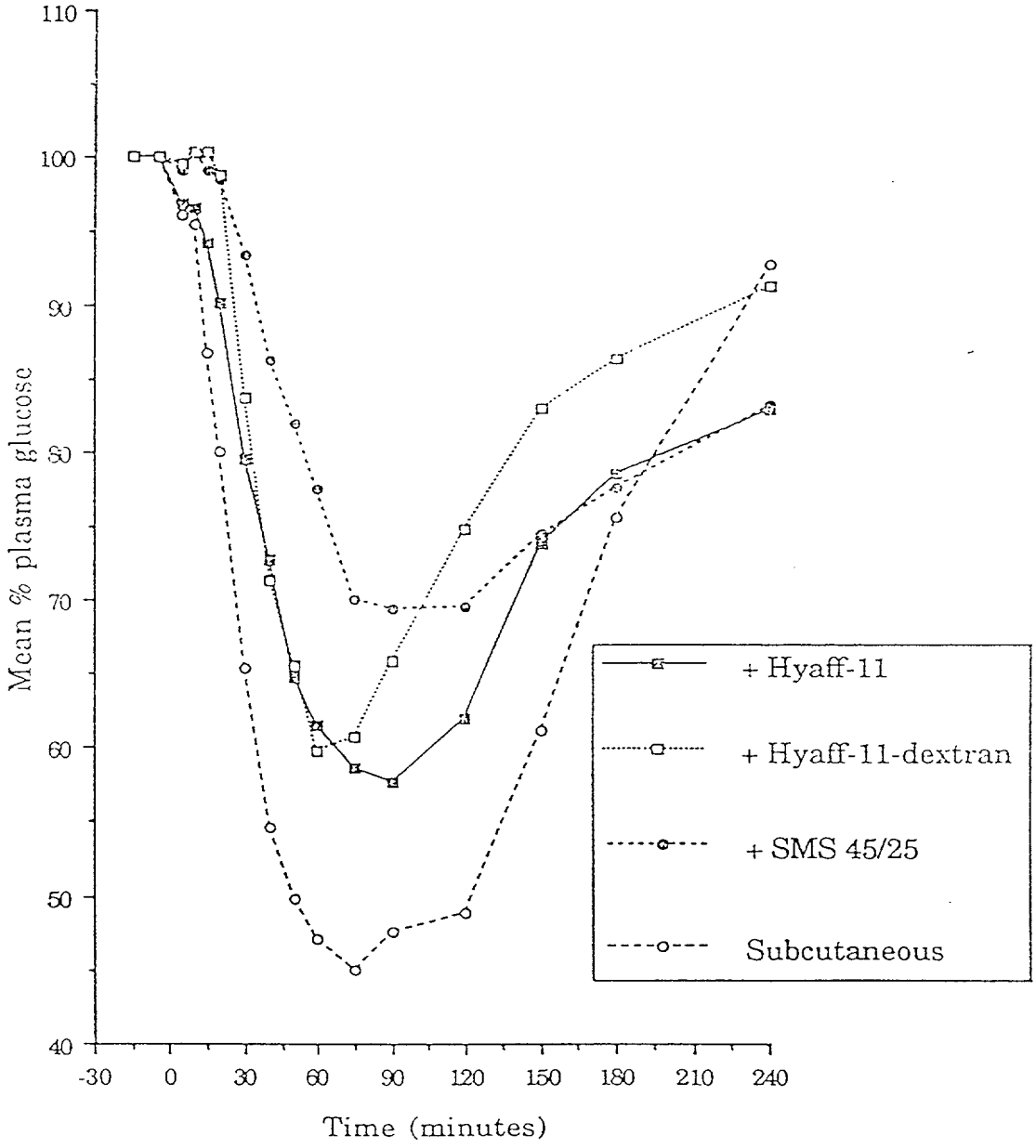

110
100
90
80
70
60
50
40
Mean % plasma glucose
-30
0
30
60
90
120
150
180
210
240
Time (minutes)
+ Hyaff-11
+ Hyaff-11-dextran
+ SMS 45/25
Subcutaneous

Figure 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Lisbeth Illum	
Serial No.:	08/359,937 Continuation of U.S.S.N. 08/065,676	Art Unit:
Filed:	December 20, 1994	Examiner:
For:	SMALL PARTICLE COMPOSITIONS FOR INTRANASAL DRUG DELIVERY	

Commissioner of Patents
and Trademarks
Washington, D. C. 20231

POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST
AND REVOCATION OF PRIOR POWERS

Sir:

As owner of the entire interest of the above-identified patent application, all powers of attorney previously given are hereby revoked and the following attorneys are hereby appointed to prosecute and transact all business in the Patent and Trademark Office connected therewith:

Patrea L. Pabst	Registration No. 31,284
Madeline I. Johnston	Registration No. 36,174

Please send all correspondence relating to the above patent application to

Patrea L. Pabst
ARNALL GOLDEN & GREGORY
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3400

Please direct all telephone calls to:

Patrea L. Pabst (404) 873-8794

The undersigned signatory, Lisbeth Illum, states that he/she is empowered to act on behalf of Danbiosyst UK Limited,

that he/she has reviewed the evidentiary documents establishing ownership of the above-identified application by Danbiosyst UK Limited, and certifies that, to the best of his/her knowledge and belief, title is in Danbiosyst UK Limited.

Danbiosyst UK Limited

By: _____

Title: MANAGING DIRECTOR

Date: 17 Feb 95

180463.1

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Serial No.: 08 / 065,676 Group No.:

Filed: May 21, 1993 Examiner:

For: Lisbeth Illum "Small Particle Compositions For Intranasal Drug Delivery"

Commissioner of Patents and Trademarks

Washington, D.C. 20231

ATTENTION: Application Division

COMPLETION OF FILING REQUIREMENTS

(check and complete this item, if applicable)

I. [X] This replies to the Notice to File Missing Parts of Application (PTO-1533) mailed June 22, 1993

NOTE: If these papers are filed before the office letter issues adequate identification of the original papers should be made, e.g., in addition to the name of the inventor and title of invention, the filing date based on the "Express Mail" procedure, the serial number from the return post card or the attorney's docket number added.

[X] A copy of the Notice to File Missing Parts of Application—Filing Date Granted (Form PTO-1533) is enclosed.

NOTE: The PTO requires that a copy of Form PTO-1533 be returned with the response to the notice to file missing parts to the application.

DECLARATION OR OATH

II. [X] No original declaration or oath was filed and enclosed is the original declaration or oath for this application.

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being transmitted therewith) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Anna-louise Owens

(Type or print name of person mailing paper)

Date: July 9, 1993

Anna-Louise Owens

(Signature of person mailing paper)

OR

☐ The original declaration or oath which was filed was determined to be defective. A new original oath or declaration is attached.

NOTE: 37 CFR 1.41(a) points out that "Full names must be stated, including the family name and at least one given name without abbreviation together with any other given name or initial."

NOTE: For surcharge fee for filing declaration after filing date complete item VI(3) below.

NOTE: Acceptable minimums in the declaration for identification of the specification to which it applies are the name of the inventor and (1) serial number (2) attorney docket number which was on the application as filed and the filing date (3) title of the invention and filing date (4) title of invention and reference to a specification which is attached to the declaration at the time of execution and filed with the declaration or (5) title of invention and a statement by a registered attorney that the application filed in the PTO is the application which the inventor executed by signing the declaration. If identification (4) is used it must be accompanied by a statement that the "attached" specification is a copy of the specification and any amendments thereto which were filed in the PTO to obtain the filing date; such a statement must be a verified statement if made by a person not registered to practice before the PTO. Notice of September 12, 1983 (1035 O.G. 3).

NOTE: Another minimum found acceptable in the declaration is the filing date (i.e., date of express mail) and the express mail number, useful where the serial number is not yet known. But note the practice where the express mail deposit is a Saturday, Sunday or holiday within the District of Columbia. 37 CFR 1.10(c).

(complete (c) or (d), if applicable)

Attached is a

(c) ☐ Statement by a registered attorney that the application filed in the PTO is the application which the inventor executed by signing the declaration.

(d) ☐ Statement that the "attached" specification is a copy of the specification and any amendments thereto which were filed in the PTO to obtain the filing date.

AMENDMENT CANCELLING CLAIMS

III. ☐ Cancel claims _____ inclusive.

TRANSMITTAL OF ENGLISH TRANSLATION OF NON-ENGLISH LANGUAGE PAPERS

IV.

☐ Submitted herewith is a verified English translation of the non-English language application papers as originally filed. It is requested that this translation be used as the copy for examination purposes in the PTO.

NOTE: For fee processing a non-English application complete item VI(5) below.

NOTE: A non-English oath or declaration in the form provided or approved by the PTO need not be translated. 37 CFR 1.69(b).

NOTE: The translation for a regular application filed in a foreign language must be verified. 37 CFR 1.52(d).

SMALL ENTITY STATUS

V.

☒ A verified statement that this filing is by a small entity

NOTE: If an original verified statement and a refund request is filed within two months of the date of payment of a fee then the excess fee paid will be refunded on request. 37 CFR 1.28(a).

(check and complete applicable items)

[X] is attached

[X] a separate refund request accompanies this paper

[ ] was filed on _____ (*original*)

COMPLETION FEES

VI.

WARNING: *Failure to submit the surcharge fees where required will cause the application to become abandoned. 37 CFR 1.53(d).*

NOTE: The filing fees, fees for claims and surcharge fees listed below in items 1, 2 and 3 are reduced by 50% where proof of a small entity status is established on or before the date the fee is paid. If the full fee was paid but a verified statement is filed within 2 months of the date of timely payment of a fee then the excess fee paid will be refunded on request. 37 CFR 1.28(a).

1. Filing fee

[ ] original patent application (37 CFR 1.16 (a))—$690.00; Small entity—$345.00 $ _____

[ ] design application (37 CFR 1.16(f))—$280.00; small entity—$140.00 $ _____

$ _____

2. fees for claims

[ ] each independent claim in excess of 3 (37 CFR 1.16(b)—$72.00; small entity—$36.00) $ _____

[ ] each claim in excess of 10 (37 CFR 1.16 (c)—$20.00; small entity—$10.00) $ _____

[ ] multiple dependent claim(s) (37 CFR 1.16 (d)—$220.00; small entity—$110.00) $ _____

3. surcharge fees

[ ] late payment of filing fee

and/or

[X] late filing of original declaration or oath (37 CFR 1.16(e)—$130.00; small entity—$65.00); 65 $ _____

NOTE: Even where a facsimile declaration or oath signed by the inventor(s) was part of the originally filed papers the surcharge fee is required.

NOTE: If both the filing fee and declaration or oath were missing from the original papers only one surcharge fee for both need be paid. 37 CFR 1.16(e).

4. [ ] petition and fee for filing by other than all the inventors or a person not the inventor (1.47—$130.00) $ _____

5. [ ] fee for processing an application filed with a specification in a non-English language (37 CFR 1.17(k) and 1.52(d)—$130.00) $ _____

6. ☐ fee for processing and retention of application (37 CFR 1.21(l)and 1.53(d)—$300.00) $ _____

NOTE: 37 CFR 1.21(l) establishes a fee for processing and retaining any application which is abandoned for failing to complete the application pursuant to 37 CFR 1.53(d) and this, as well as, the changes to 37 CFR 1.53 and 1.78 indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee or the processing and retention fee of § 1.21(1) within 1 year of notification under §1.53(d) must be paid.

Total completion fees $ 65

EXTENSION OF TIME

VII.

(complete (a) or (b) as applicable)

The proceedings herein are for a patent application and the provisions of 37 CFR 1.136(a) apply.

(a) ☐ Applicant petitions for an extension of time, the fees for which are set out in 37 CFR 1.17(a)-(d), for the total number of months checked below:

Extension (months)	Fee for other than small entity	Fee for small entity
☐ one month	$ 110.00	$ 55.00
☐ two months	$ 350.00	$175.00
☐ three months	$ 810.00	$405.00
☐ four months	$1,280.00	$640.00

Fee $_____

If an additional extension of time is required please consider this a petition therefor.

(check and complete the next item, if applicable)

☐ An extension for ____ months has already been secured and the fee paid therefor of $_____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $_____

or

(b) ☐ Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

TOTAL FEE DUE

VIII.

The total fee due is

Completion fee(s) $ 65

Extension fee (if any) $_____

TOTAL FEE DUE $ 65

PAYMENT OF FEES

IX.

☒ enclosed is a check in the amount of $ 65

☐ charge Account No. _____ in the amount of $_____
A duplicate of this request is attached.

NOTE: Fees should be itemized in such a manner that it is clear for which purpose the fees are paid. 37 CFR 1.22(b).

AUTHORIZATION TO CHARGE ADDITIONAL FEES

X.

WARNING: *Accurately count claims, especially multiple dependant claims, to avoid unexpected high charges if extra claims are authorized.*

☒ The Commissioner is hereby authorized to charge the following additional fees which may be required by this paper and during the pendency of this application to Account No. 12-2147 :

☒ 37 CFR 1.16 (a), (f) or (g) (filing fees)

☒ 37 CFR 1.16 (b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 CFR 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

☒ 37 CFR 1.16(e) (surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application)

☒ 37 CFR 1.17 (application processing fees)

WARNING: *While 37 CFR 1.17(a), (b), (c) and (d) deal with extensions of time under § 1.136(a) this authorization should be made only with the knowledge that: "Submission of the appropriate extension fee under 37 CFR 1.136(a) is to no avail **unless** a request or petition for extension is filed." (Emphasis added). Notice of November 5, 1985 (1060 O.G. 27).*

☐ 37 CFR 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 CFR 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 CFR 1.311(b).

NOTE: 37 CFR 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee". From the wording of 37 CFR 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

Reg. No. 20,570

Tel. No.: (617) 227-0700

Scott R. Foster
SIGNATURE OF ATTORNEY

Scott R. Foster
Type or print name of attorney

Lorusso & Loud
P.O. Address

440 Commercial St. Boston, MA 02109

ATTORNEYS DOCKET NUMBER
EPC-148

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

SMALL PARTICLE COMPOSITIONS FOR INTRANASAL DRUG DELIVERY

the specification of which

(check one) ☐ is attached hereto.

XX was filed on May 21, 1993 as

Application Serial No. 08/065,676

and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

(NUMBER)	(COUNTRY)	(DAY/MONTH/YEAR FILED)	Priority Claimed YES	NO
8924935.3	U.K.	Nov. 4, 1989	☒	☐
			☐	☐
			☐	☐

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(APPLICATION SERIAL NO.)	(FILING DATE)	(STATUS) (PATENTED, PENDING, ABANDONED)
07/842,351	Mar. 24, 1992	pending
PCT/GB90/01676	Nov. 1, 1990	

If more space is needed for any of the above categories, please continue on an additional form and SIGN.

I HEREBY APPOINT THE FOLLOWING AS MY ATTORNEY OR AGENT(S) WITH FULL POWER OF SUBSTITUTION TO PROSECUTE THIS APPLICATION AND TRANSACT ALL BUSINESS IN THE PATENT OFFICE CONNECTED THEREWITH:

Name	Reg. No.	Name	Reg. No.	Name	Reg. No.
Anthony M Lorusso	25,059	Barbara A. Barakat	32,190	Scott R. Foster	20,570
George A. Loud	25,814	Anne I. Craig	32,976		
Arthur A. Smith, Jr.	24,178	Thomas M. Saunders	29,585		

SEND CORRESPONDENCE TO:

NAME	PHONE NO.	STREET	CITY & STATE	ZIP CODE
Lorusso & Loud	(617) 227-0700	440 Commercial Street	Boston MA	02109

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

LISTING OF APPLICANTS CONTINUED ON PAGE 2 HEREOF. ☐ YES ☐ NO

Full name of sole or first inventor Lisbeth ILLUM

Inventor's signature _____ Date _____

Residence 19 Cavendish Crescent North, The Park, Nottingham, NG7 1BA, England

Citizenship Denmark

Post Office Address same as above

Full name of second joint inventor, if any _____

Second Inventor's signature _____ Date _____

Residence _____

Citizenship _____

Post Office Address _____

Full name of third joint inventor, if any _____

Inventor's signature _____ Date _____

Residence _____

Citizenship _____

Post Office Address _____

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

☒ **In re application of*:** Lisbeth Illum

Serial No.: 0 8/065,676 **Group No.:**

Filed: May 21, 1993 **Examiner:**

For*: "Small Particle Compositions For Intranasal Drug Delivery"

☐ **Patent No.:** **Issued:**

**NOTE:* *Insert name(s) of inventor(s) and title also for patent. Where the refund request is with respect to a maintenance fee payment also insert application serial number and filing date and add Box M. Fee to address.*

Commissioner of Patents and Trademarks
Washington, D.C. 20231

ATTENTION: Refund Section, Accounting Division, Office of Finance

REQUEST FOR REFUND
(37 C.F.R. 1.28(a))

I. SUBMISSION OF VERIFIED STATEMENT

(Complete (a) or (b))

(a) ☒ Attached is a verified statement claiming small entity status in this application.

(b) ☐ A verified statement claiming small entity status was filed in this application on _____

II. REFUND REQUEST

This request for refund is made within two months of the date a fee was paid in this application on May 21, 1993 in the amount of $ $355

NOTE: The two-month period (§ 1.28(a)) is not included in the provisions for extension under 37 C.F.R. 1.136 since it is not a period for response. Notice of November 30, 1983, 49 FR 548, January 4, 1984.

CERTIFICATE OF MAILING (37 CFR 1.8(a))

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Anna-Louise Owens
(Typed or printed name of person mailing paper)

Date: July 9, 1993

Anna Louise Owens
(Signature of person mailing paper)

III. FEES PAID FOR WHICH REFUND REQUESTED

	AMOUNT OF REFUND REQUESTED
☒ filing fee	$ 355
☐ surcharge for filing the basic filing fee on a date later than the filing date of the application (37 CFR 1.16(e))	$
and/or	
☐ surcharge for filing the oath or declaration on a date later than the filing date of the application (37 CFR 1.16(e))	$
☐ extension of term	$
☐ issue fee	$
☐ patent maintenance fee	
☐ first maintenance fee	$
☐ second maintenance fee	$
☐ third maintenance fee	$
☐ patent maintenance fee surcharge.	

NOTE: The refund provisions of § 1.28(a) for later submitted small entity statements apply to maintenance fees. Notice of July 30, 1984, 1046 O.G. 28-37.

☐ other $

TOTAL REFUND REQUESTED $ 355

IV. MANNER OF REFUND

Please make refund by

☒ crediting Account No. 12-2147

☐ refunding overpayment

Signature of attorney

Scott R. Foster

Type or print name of attorney

Reg. No.: 20,570

Lorusso & Loud

Tel. No.: (617) 227-0700

P.O. Address

440 Commercial St. Boston, MA 02109

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

☒ In re application of*:

Serial No.: 08/065,676 Group No.:

Filed: May 21, 1993 Examiner:

For*: "Small Particle Compositions For Intranasal Drug Delivery"

☐ Patent No.: Issued:

Lisbeth Illu

*NOTE: *Insert name(s) of inventor(s) and title also for patent. Where submission is with respect to a maintenance fee payment also insert application serial number and filing date and mark Form Box M. Fee.*

Commissioner of Patents and Trademarks
Washington, D.C. 20231

SUBMISSION OF VERIFIED STATEMENT(S) TO ESTABLISH SMALL ENTITY STATUS

The attached statement is being submitted to establish small entity status in this

☒ application

☐ patent

by the:

(check all applicable boxes below)

a.	☐	independent inventor(s)	37 CFR 1.9(c) and 1.27(b)
b.	☐	non-inventor supporting claim by author	37 CFR 1.9(c) and 1.27(b)
c.	☒	small business concern	37 CFR 1.9(d) and 1.27(c)
d.	☐	non-profit organization	37 CFR 1.9(e) and 1.27(d)

Reg. No. 20,570

Tel. No. (617) 227-0700

Scott R. Foster

SIGNATURE OF ATTORNEY

Scott R. Foster

Type or print name of attorney

Lorusso & Loud

P.O. Address

440 Commercial St. Boston, MA 02109

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231

Anna-louise Owens

(Type or print name of person mailing paper)

Date: July 9, 1993

Anna-louise Owens

(Signature of person mailing paper)

PATENT

Attorney's Docket No. EPC-148

Applicant or Patentee: Lisbeth Illum

Serial or Patent No.: 0 8/ 065,676

Filed or Issued: May 21, 1993

For: "Small Particle Compositions For Intranasal Drug Delivery"

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(c))—SMALL BUSINESS CONCERN

I hereby declare that I am

- ☐ the owner of the small business concern identified below:
- ☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN Danbiosyst UK Limited

ADDRESS OF CONCERN 6 William Lee Building, Highfields Science Park, Nottingham, NG7 2RQ, England

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third-party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed, to and remain with the small business concern identified above with regard to the invention, entitled "Small Particle Compositions For Intranasal Drug Delivery"

by inventor(s) Lisbeth Illum

described in

- ☐ the specification filed herewith.
- ☒ application serial no. 08 / 065,676, filed May 21, 1993.
- ☐ patent no. _____, issued _____.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

*NOTE: *Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27).*

NAME _____

ADDRESS _____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

NAME _____

ADDRESS _____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small business entity is no longer appropriate. (37 CFR 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Lisbeth Illum

TITLE OF PERSON OTHER THAN OWNER Managing Director

ADDRESS OF PERSON SIGNING 19 Cavendish Crescent North, The Park, Nottingham, NG7 1BA, England

SIGNATURE _____ Date 4 May 1993

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Lisbeth Illum	
Serial No.:	Divisional of U.S.S.N. 08/359,937	Group Art Unit: To be assigned
Filed:	June 17, 1997	Examiner: To be assigned
For:	SMALL PARTICLE COMPOSITIONS FOR INTRANASAL DRUG DELIVERY	

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to examination of the above-identified new application, the Examiner is respectfully requested to enter the following amendments:

In the Specification

On the first page, after the title, insert: --This application is a divisional of U.S. Serial Number 08/359,937, filed December 20, 1994, which is a continuation of U.S. Serial Number 08/065,676, filed May 21, 1993, now abandoned, which is a continuation in part of 07/842,351, filed March 24, 1992, now abandoned, which is the U.S. National Stage of PCT/GB90/01676, filed November 1, 1990, which corresponds to UK 8924935.3, filed November 4, 1989.--

In the Claims

Please cancel claims 13 and 14.

Please amend the claims as follows.

1. (amended) [In] a particulate drug delivery composition for intranasal delivery comprising a plurality of bioadhesive microspheres comprising a material selected from the group consisting of polysaccharides, proteins, and synthetic polymers, wherein the polysaccharide is selected from the group consisting of a starch, a dextran, a hyaluronic acid, a gellan gum and pectin and the protein is selected from the group consisting of gelatin, albumin, and collagen, and a systemically active drug selected from the group consisting of proteins and peptides, and non-protein drugs selected from the group consisting of antibiotics, anesthetics, vasoconstrictors, cardiotonics, vasodilators, antiseptics, bone metabolism controlling agents, hypotensives, sedatives, anti-tumour agents, anti-inflammatory agents, anti-histaminic agents, anti-allergic agents, and antitussive-expectorant agents, [the improvement comprising that] wherein at least 90 wt % of the microspheres of the composition have a diameter of between 0.1 μm and 10 μm, and wherein the composition is capable of systemic delivery of a therapeutically effective amount of the drug to a mammal upon intranasal administration.

3. (amended) A drug delivery composition according to Claim 1 or 2 wherein the microspheres comprise starch, [starch derivatives], gelatin, albumin, collagen, or dextran [or dextran derivatives].

6. (amended) A drug delivery composition according to Claim 1 wherein the microspheres have been [stabilised by heat treatment] heated to stabilize the microspheres.

8. (amended) A drug delivery composition according to Claim 7 wherein the absorption enhancer is a surfactant [a lysophosphatidylcholine or a lysophosphatidylglyrerol].

Please add the following new claims.

15. (new claim) The drug delivery composition of claim 1 wherein the microspheres comprise a material or ester thereof selected from the group consisting of polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid, gellan gum and pectin.

16. (new claim) The drug delivery composition of claim 1 wherein the microspheres comprise a material selected from the group consisting of hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch and grafted starch.

Remarks

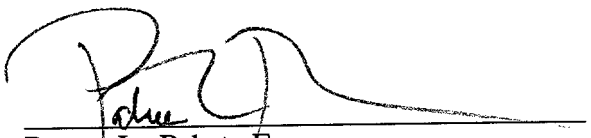
A Terminal Disclaimer to the previously issued patent, U.S. Patent No. 5,204,108, is enclosed. Claim 1 has been amended to define the material forming the microspheres as comprising the materials described in the application at page 5, line 1, to page 6, line 5,

(where the terms starch and dextran include the derivatives recited in dependent claims 3, 4, and 16 and described at page 5, lines 15-30). Claim 1 has also been amended to recite that the drug is either a protein or peptide or one of the recited classes of drugs described at page 14, lines 9-30, which excludes sodium chromoglycate. No new matter has been added.

Allowance of claims 1-12, 15 and 16, as amended, is earnestly solicited. A copy of all claims as pending upon entry of this amendment is attached to facilitate review by the examiner.

Please credit any overpayment or charge any other fees due in connection with this matter to our deposit account No. 01-2507. A duplicate of this transmittal is enclosed to facilitate this process.

Respectfully submitted,



Patrea L. Pabst, Esq.
Registration No. 31,284

Date: June 17, 1997

ARNALL GOLDEN & GREGORY LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8794
(404) 873-8795 (fax)

APPENDIX: *Pending Claims Upon Entry of Amendment*

1. (amended) A particulate drug delivery composition for intranasal delivery comprising a plurality of bioadhesive microspheres comprising a material selected from the group consisting of polysaccharides, proteins, and synthetic polymers, wherein the polysaccharide is selected from the group consisting of a starch, a dextran, a hyaluronic acid, a gellan gum and pectin and the protein is selected from the group consisting of gelatin, albumin, and collagen, and a systemically active drug selected from the group consisting of proteins and peptides, and non-protein drugs selected from the group consisting of antibiotics, anesthetics, vasoconstrictors, cardiotonics, vasodilators, antiseptics, bone metabolism controlling agents, hypotensives, sedatives, anti-tumour agents, anti-inflammatory agents, anti-histaminic agents, anti-allergic agents, and antitussive-expectorant agents, wherein at least 90 wt % of the microspheres of the composition have a diameter of between 0.1 μm and 10 μm, and wherein the composition is capable of systemic delivery of a therapeutically effective amount of the drug to a mammal upon intranasal administration.

2. A drug delivery composition according to Claim 1 wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface.

3. (amended) A drug delivery composition according to Claim 1 or 2 wherein the microspheres comprise starch, gelatin, albumin, collagen, or dextran.

4. A drug delivery composition according to Claim 3 wherein the microspheres are starch microspheres.

5. A drug delivery composition according to Claim 1 wherein the microsphere material is cross-linked.

6. (amended) A drug delivery composition according to Claim 1 wherein the microspheres have been heated to stabilize the microspheres.

7. A drug delivery composition according to Claim 1 additionally comprising an absorption enhancer.

8. (amended) A drug delivery composition according to Claim 7 wherein the absorption enhancer is a surfactant.

9. A drug delivery composition according to Claim 1 wherein the drug is a biologically active peptide.

10. A drug delivery composition according to Claim 9 wherein the peptide is insulin or calcitonin.

11. A system for intranasal drug delivery comprising a drug delivery composition according to Claim 1 and a container having an orifice through which the composition can be delivered to the nasal mucosa in a gas stream.

12. A system according to Claim 11 wherein the system is such that, in use, the product of the flow rate and the square of the microsphere aerodynamic diameter is greater than 2000 μm^2.litres/min.

15. (new claim) The drug delivery composition of claim 1 wherein the microspheres comprise a material or ester thereof selected from the group consisting of polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid, gellan gum and pectin.

16. (new claim) The drug delivery composition of claim 1 wherein the microspheres comprise a material selected from the group consisting of hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch and grafted starch.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Lisbeth Illum	
Serial No.:	Divisional of U.S.S.N. 08/359,937	Group Art Unit: To be assigned
Filed:	June 17, 1997	Examiner: To be assigned
For:	SMALL PARTICLE COMPOSITIONS FOR INTRANASAL DRUG DELIVERY	

Assistant Commissioner for Patents
Washington, D.C. 20231

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3. (amended) A drug delivery composition according to Claim 1 or 2 wherein the microspheres comprise starch, [starch derivatives], gelatin, albumin, collagen, or dextran [or dextran derivatives].

6. (amended) A drug delivery composition according to Claim 1 wherein the microspheres have been [stabilised by heat treatment] heated to stabilize the microspheres.

8. (amended) A drug delivery composition according to Claim 7 wherein the absorption enhancer is a surfactant [a lysophosphatidylcholine or a lysophosphatidylglyrerol].

Please add the following new claims.

15. (new claim) The drug delivery composition of claim 1 wherein the microspheres comprise a material or ester thereof selected from the group consisting of polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid, gellan gum and pectin.

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Remarks

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(where the terms starch and dextran include the derivatives recited in dependent claims 3, 4, and 16 and described at page 5, lines 15-30). Claim 1 has also been amended to recite that the drug is either a protein or peptide or one of the recited classes of drugs described at page 14, lines 9-30, which excludes sodium chromoglycate. No new matter has been added.

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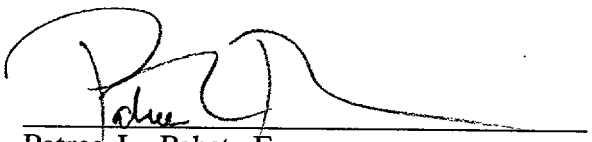
Please credit any overpayment or charge any other fees due in connection with this matter to our deposit account No. 01-2507. A duplicate of this transmittal is enclosed to facilitate this process.

Respectfully submitted,



Patrea L. Pabst, Esq.
Registration No. 31,284

Date: June 17, 1997

ARNALL GOLDEN & GREGORY LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8794
(404) 873-8795 (fax)

APPENDIX: *Pending Claims Upon Entry of Amendment*

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2. A drug delivery composition according to Claim 1 wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface.

3. (amended) A drug delivery composition according to Claim 1 or 2 wherein the microspheres comprise starch, gelatin, albumin, collagen, or dextran.

4. A drug delivery composition according to Claim 3 wherein the microspheres are starch microspheres.

5. A drug delivery composition according to Claim 1 wherein the microsphere material is cross-linked.

6. (amended) A drug delivery composition according to Claim 1 wherein the microspheres have been heated to stabilize the microspheres.

7. A drug delivery composition according to Claim 1 additionally comprising an absorption enhancer.

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16. (new claim) The drug delivery composition of claim 1 wherein the microspheres comprise a material selected from the group consisting of hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch and grafted starch.

CERTIFICATE UNDER 37 C.F.R. § 3.73(b)

Patentees: Lisbeth Illum

U.S.Patent Application No.: Divisional of 08/359,937 Issued: To be Assigned

For: SMALL PARTICLE COMPOSITIONS FOR INTRANASAL DRUG DELIVERY

Danbiosyst U.K. Limited, a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of:

An assignment of the patent application identified above from Lisbeth Illum to Danbiosyst U.K. Limited, was recorded in the Patent and Trademark Office at Reel 6719, Frame 0465-0466.

OR

A chain of title from the inventor(s), of the patent application identified above, to the current assignee as shown below:

1. From: _____ To: _____
The document was recorded in the Patent and Trademark Office at Reel ____, Frame ____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the Patent and Trademark Office at Reel ____, Frame ____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplement sheet.

[ ] Copies of assignments or other documents in the chain of title are attached.

The undersigned has reviewed all the documents in the chain of title of the patent application identified above and, to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date : June 17, 1997

Name : Patricia L. Tabst

Title : Atty of Record Reg. No. 31,284

Signature : _____